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USE OF ADENOSINE DEAMINASE INHIBITORS TO TREAT SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

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This application claims priority to co-pending PCT/US00/13987, filed May 22, 2000 and U.S. Serial No. 09/317,678 filed May 24, 1999, now U.S. Patent No. 6,103,702.

This invention relates to a new use of adenosine deaminase inhibitors in the prevention or treatment of adverse consequences of systemic inflammatory responses (SIRS). These conditions are ameliorated by increasing the local concentration of adenosine in affected regions.

BACKGROUND OF THE INVENTION

Conditions resulting in or from a systemic inflammatory response syndrome (SIRS) are associated with an exaggerated immune response, oxygen free-radical-mediated injury, and tissue perfusion maldistribution. Such conditions include endotoxin shock, septic shock, sepsis, endotoxemia, septicemia, peritonitis, and adult respiratory distress syndrome (ARDS). Current treatment is unsatisfactory. Therapeutic attempts to modify cytokine responses during SIRS-related conditions have focussed on antibodies to the cytokines or cytokine receptor antagonists. These approaches have proven unsuccessful because some level of cytokine response is required for survival from SIRS-related conditions.

Adenosine has been reported to be an endogenous modulator of inflammation by virtue of its effects on stimulated granulocyte function (Cronstein *et al.*, 1986) and on macrophage, lymphocyte and platelet function. Adenosine receptor agonists have been reported to be beneficial in an experimental model of inflammation (Schrier *et al.*, 1990). Adenosine and a related analog have been reported to inhibit in vitro production of the cytokine, tumor necrosis factor α (Parmely *et al.*, 1991). Antibodies to TNF-α have not been shown to alter mortality in sepsis (Abraham *et al.*, 1998; Cohen *et al.*, 1996; and Amiot *et al.*, 1997).

Adenosine is an endogenous, ubiquitous molecule that modulates immune function, can suppress or increase free-radical production, and produces vasodilation in regions wherein adenosine is produced in significant quantities.